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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,772	OCHIAI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 3/16/09.

Claims 2 and 12-15 were canceled.

Claims 1 and 3-11 remain pending and are under consideration.

Rejections not reiterated are withdrawn.

Priority

In the response filed 3/16/09, Applicant indicates that a certified translation was attached, however, no translation was received by the Office. Accordingly, the effective filing date of the instant claims is no earlier than the filing date of PCT/JP2005/05786, i.e. 3/26/05 because, although Applicant claims priority to JAPAN 2004-107512, filed 3/31/2004, and a copy of this foreign priority document is in the file, no translation of this Japanese language document has been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 6-9, and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of

record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record).

Certik taught that there was an increasing demand for biologically active polyunsaturated fatty acids (PUFAs) and that oleaginous filamentous fungi possess several advantages as a source for PUFAs. In particular, *Mortierella alpina* is disclosed as one of the best producers of various types of PUFA, and is a strain which has several advantages including: it is a highly oleaginous strain; its lipogenesis is simply regulated; it is one of the most well-studied microorganisms producing PUFAs; the strain is able to incorporate and transform exogenous fatty acids; it is amenable to molecular-genetic study; and the strain can be used in an industrial scale. Certik also disclosed the use of such fungi for producing lipids, wherein fatty acid desaturase activity was decreased by mutation or by use of specific enzyme inhibitors. See abstract, paragraph bridging left and right columns on page 500; paragraph bridging pages 500 and 501; page 501, left column, first full paragraph; and Fig. 1 on page 501. More specifically, Certik noted that mutants with defective desaturases such as Δ^5, Δ^6, Δ^9, Δ^{12}, and ω^3 are worthwhile as producers of useful PUFAs, and for providing valuable information on PUFA biosynthesis in *M. alpina*. Page 501, left column, last paragraph.

Ueda taught that RNAi provided a means of selectively inhibiting expression of genes of choice that was conserved across a wide variety of organisms including plants animals and fungi. Methods include stably transfecting target organisms with heritable expression constructs encoding RNAi agents. See abstract; page 195, second full

paragraph; Fig. 1B on page 196; last paragraph on page 197; and second full paragraph on page 199.

Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000) taught means for delivering genetic material to *Mortierella* for stable expression of genes of interest. See abstract, and "Vector construction and transformation of *M. alpina"* at page 4656.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use RNAi to inhibit the activity of any of the Δ^5, Δ^6, Δ^9, Δ^{12}, or ω^3 desaturases of *M. alpina*. One would have been motivated to inhibit these enzymes because Certik indicated that strains defective in these enzymes were useful as producers of PUFAs as well as for providing valuable information on PUFA biosynthesis. It would have been obvious to use siRNA to suppress expression of the genes because use of this method allows one to specifically and selectively target any desaturase gene of interest for which target sequence information was available, obviating the need to screen for randomly occurring mutants. Further, one would have had a reasonable expectation of success in view of the fact that RNA interference was known to function in fungi (see Ueda) , and in view of the availability of vectors and techniques for establishing stable expression of heterologous genes in *M. alpina* (see Mackenzie).

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takeno et al (Appl. Microbiol. Biotechnol. 65: 419-425, 2004) as applied to claim 1

above, and further in view of Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record) and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record).

Takeno disclosed the establishment of a microprojectile bombardment-based transfection system of M. alpina, and the establishment of stable transfectants. See abstract. The authors also stated that they "have aimed to overexpress or destroy a gene involved in PUFA biosynthesis". Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the method of Takeno to suppress the expression of a PUFA biosynthetic gene by destroying the gene, as suggested by Takeno.

Takeno did not disclose the use of RNAi.

Ueda taught that RNAi provided a means of selectively inhibiting expression of genes of choice that was conserved across a wide variety of organisms including plants, animals, and fungi. Methods include transfecting target organisms with heritable expression constructs encoding RNAi agents. See abstract; page 195, second full paragraph; Fig. 1B on page 196; last paragraph on page 197; and second full paragraph on page 199.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA to inhibit expression of a PUFA biosynthesis gene. One of ordinary skill appreciates that genetic methods for physically destroying a gene require recombination events at a precise site, i.e. the site of the gene of interest. However, Mackenzie taught that it was difficult to obtain stable, chromosomally-integrated transformants in *M. alpina*, and that to do so it was necessary to take advantage of the

large number of repetitive rDNA sites in the *M. alpina* genome by targeting them for homologous recombination. See page 4655, right column, second sentence of first full paragraph. *M. alpina* contains 150-200 tandemly repeated copies of the rDNA locus per haploid genome. Use of vectors designed to integrate at rDNA loci increases the probability of obtaining stable integrants. See page 4658, left column, first full paragraph, and right column, lines 3-9. Thus one of ordinary skill would conclude that there would be a greater expectation of success in suppressing expression of a target gene if one used siRNA expression vectors targeted to integrate in *M. alpina* rDNA, than if one sought to knock out a specific *M. alpina* gene by homologous recombination. Thus the invention as a whole was prima facie obvious.

Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record) as applied to claims 1, 3, 4, 6-9, and 11 above, and further in view of White et al (US 6,939,704).

The teachings of Certik, Ueda, and Mackenzie are discussed above and can be combined to render obvious methods of suppressing the expression of a PUFA biosynthetic gene in *M. alpina* using RNAi methodology.

These references did not teach gene delivery by electroporation or particle bombardment.

White taught that filamentous fungi could be transfected by several methods including calcium chloride treatment of protoplasts, electroporation, and particle bombardment. See column 12, lines 22-31

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of calcium chloride treatment of protoplasts, electroporation, or particle bombardment to deliver nucleic acids to M. alpina, because these techniques were suggested for use with filamentous fungi.

Thus the invention as a whole was prima facie obvious.

Claims 9 and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Certik et al (Trends in Biotechnology 16(12): 500-505, 1998, of record), Ueda (J. Neurogenetics 15(3-4): 193-204, 2001, of record), and Mackenzie et al (App. Env. Microbiol. 66(1): 4655-4661, 2000, of record) as applied to claims 1, 3, 4, 6-9, and 11 above, and further in view of Parker-Barnes et al (Proc. Nat. Acad. Sci. USA 97(15): 8284-8289, 2000, of record).

The teachings of Certik, Ueda, and Mackenzie are discussed above and can be combined to render obvious methods of suppressing the expression of a PUFA biosynthetic gene in *M. alpina* using RNAi methodology. Certik also disclosed that fatty acid elongase was required in PUFA biosynthesis.

Parker-Barnes discovered a gene encoding a fatty acid elongase gene from *M. Alpina*.

It would have been obvious to one of ordinary skill in the art at the time of the invention to suppress expression of the M. alpina elongase gene of Parker-Barnes using RNAi methodology. One would have been motivated to do so in order to evaluate the function of the gene and its interactions with other genes in the fatty acid biosynthesis pathway. See e.g. Ueda, abstract.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 3/16/09 have been fully considered but they are not persuasive.

At page 6 of the response, Applicant argues that the rejection is improper because none of the references teaches a cosuppression method as presently recited. This is incorrect. First, it should be noted that the claims do not require a cosuppression step *per se* because they recite RNAi and cosuppression steps as alternatives. Therefore the cited art can render the claims obvious without teaching a cosuppression step, as long as it teaches an RNAi step, which it does. Second, those of skill in the art appreciate that RNAi is a species of the genus of phenomena recognized as cosuppression, which includes modulation of gene expression at the transcriptional level (e.g. DNA methylation), and the posttranscriptional level (e.g. post transcriptional gene silencing (PTGS) or quelling). PTGS and quelling are indistinguishable from RNAi. See e.g. Thakur (Electronic J. Biotechnol. 6(1): 39-49, 2003, at pages 3 and 4 of PDF) or Robert et al (Genes Dev. 19:782-787, 2005) in which the authors indicate that

cosuppression is a dsRNA-induced RNAi-mediated silencing (paragraph bridging pages 785 and 786). Thus RNAi can be broadly interpreted as a "cosuppression step" required by the instant claims. Therefore, the cited art teaches both of the alternatives recited in the claims.

Applicant argues at pages 6 and 7 that there was no reasonable expectation of success in combining the cited references. For support, Applicant relies on the instant specification at the paragraph bridging pages 6 and 7, which indicates that it cannot be known whether RNAi will be effective in a specific organism until the method is actually carried out. This is unpersuasive. It is not necessary to know with certainty whether or not a method will work in order to establish a prima facie case of obviousness. Instead, the standard is whether or not there would have been a reasonable expectation of success. The cited art indicates that RNAi pathways were conserved across three phylogenetic kingdoms, including plants, animals, and fungi. If the pathway is conserved across different phylogenetic kingdoms, then it is considered far more likely than not that it will be conserved within a single kingdom. Therefore, because RNAi pathways were known to exist in fungi, there would have been a reasonable expectation that the fungal species *M. alpina* would have a functional RNAi pathway, and that one could carry out RNAi in this species. In light of the evidence presented by Ueda, the burden has been shifted to Applicant to provide evidence or reasoning that there would have been no reasonable expectation of success. The statement in the specification that it could not be known for certain whether or not the method would work in *M. alpina* does not address the level of expectation of success, and certainty of success is not

required to establish a prima facie case of obviousness. Furthermore, the statement in the specification is not supported by any evidence. In contrast, the rejection relies on the evidence of Ueda. In the absence of evidence or reasoning to the contrary, the evidence of Ueda provides a reasonable expectation of success.

Applicant states that the Office appears to use improper hindsight to pick an choose the various elements to achieve the specific invention. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See MPEP 2145 (IX)(A). Applicant has not pointed to any claim limitation that was met by using knowledge gleaned only from the applicant's disclosure, and not the prior art, so the argument of improper hindsight is unpersuasive.

At pages 7 and 8 Applicant argues that the cited art does not teach fine tuning of expression by partial suppression, and that it teaches only complete knock out of expression. If this is an argument of non-obviousness for failure to teach claim limitations, then it is unpersuasive because Applicant is arguing limitations that are not in the claims. The claims do not recite or require partial suppression. To the extent that it is an argument of unexpected results, it is unpersuasive because Applicant has presented no evidence that partial suppression of expression is in any way unexpected when performing RNAi. To support the position that the results are unexpected, Applicant relies on a statement in Ueda at page 201 which indicates that RNAi provides

a powerful tool for "knocking out" the activity of specific genes. This statement provides no evidence that RNAi must always provide an absolute inhibition of gene expression. In fact, in the last full paragraph on page 201 Ueda referred to objective evidence that RNAi need not always provide complete inhibition, noting that inhibition in several mammalian cell lines (NIH 3T3, COS-7, and HeLa) was incomplete. Furthermore, Ueda taught that the efficiency of RNAi varies with the dsRNA length and cell type (see sentence bridging pages 196 and 197). Thus the evidence of record supports the position that RNAi can yield partial suppression, and there is no evidence of record to support the position that partial suppression by RNAi is an unexpected result.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635